The Clinical Value of Proposed Risk Stratification Tools in Pediatric Pulmonary Arterial Hypertension

Haarman, Meindina G.; Douwes, Johannes M.; Ploegstra, Mark-Jan; Roofthooft, Marcus T. R.; Vissia-Kazemier, Theresia R.; Hillege, Hans L.; Berger, Rolf M. F.

Published in:
American Journal of Respiratory and Critical Care Medicine

DOI:
10.1164/rccm.201902-0266LE

Publication date:
2019

The clinical value of proposed risk stratification tools in pediatric pulmonary arterial hypertension

Meindina G. Haarman, MD[1]; Johannes M. Douwes, MD, PhD[1]; Mark-Jan Ploegstra, MD, PhD[1]; Marcus T.R. Roofthooft, MD, PhD[1]; Theresia R. Vissia-Kazemier, RN MANP[1]; Hans L. Hillege, PhD[2,3]; Rolf M.F. Berger, MD, PhD[1]

Affiliations:

[1]Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[2]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[3]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Sources of Funding: This study was supported by the Sebald fund

Correspondence:

Meindina G. Haarman, MD, Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen
P.O. Box 30 001, 9700 RB Groningen, the Netherlands.
Office phone: +31(0)50 361 3363. Fax: +31(0)50 361 4235. E-mail: m.g.haarman@umcg.nl

Word count: 1558

To the Editor:

Pediatric pulmonary arterial hypertension (PAH) is a rare and lethal disease. Although the availability of PAH-targeted drugs has improved the outcome of these patients, there is still a high need for optimization of treatment strategies. In this context, accurate risk stratification of patients with PAH is regarded crucial. During the World Symposium on Pulmonary Hypertension in 2013 (WSPH 2013) a pediatric task force proposed a risk stratification tool for children with PAH that stratifies children into a lower or higher risk group for mortality.[1] This model, that was then included in the guidelines for pediatric PAH from the American Heart Association and American Thoracic Society,[2] consists of variables that were selected based on either expert opinion or reported prognostic value. Although the prognostic values of several of these pediatric risk factors have been studied individually,[3] their combination in a pediatric PAH risk model and its potential use in goal-oriented treatment strategies have not been investigated before. We investigated the prognostic value of this pediatric PAH risk stratification tool, both at time of diagnosis and at one-year-follow-up. We also examined the applicability and potential clinical value of a low-risk profile as treatment target.

Children (≤18 years old with idiopathic or hereditary PAH (IPAH/HPAH)) consecutively enrolled in the prospective clinical registry of the National Referral Center for Pediatric Pulmonary Hypertension in the Netherlands between 1993 and 2017 were included in the study. All patients had a standardized diagnostic work-up at presentation and were followed prospectively using a standardized protocol. Ethical approval for this ongoing registry was obtained from the Medical Ethics Review Board of the University Medical Center Groningen and written informed consent, from the patients and/or their guardians, was given at enrollment. Diagnosis of PAH was confirmed with right heart catheterization (RHC) or in case of clinical instability with echocardiography (n=4). For this study we assessed two versions of the risk stratification model based on the number of low-risk criteria. First, we

tested the full model proposed at the WSPH 2013, augmented with two extra variables, systemic venous oxygen saturation (SvO_2) and right atrial area (RA-area), extracted from the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines and proven to be prognostic for outcome also in pediatric PAH.[4–8] This resulted in a total of 13 low-risk criteria: absence of syncope, height z-score >-2, body mass index (BMI) z-score >-2, World Health Organization Functional Class (WHO-FC) I/II, N-terminal pro-B-Type Natriuretic Peptide (NT-proBNP) ≤1200 ng/l, tricuspid plane systolic excursion (TAPSE) ≥12 mm, RA-area <18 cm², systemic cardiac index ≥2.5 l/min/m², ratio of mean pulmonary arterial pressure over mean systemic arterial pressure (mPAP/mSAP) <0.75, mean right atrial pressure (mRAP) ≤10 mmHg, pulmonary vascular resistance index (PVRi) ≤ 20 WU·m², acute responder at vasoreactivity testing according to Sitbon criteria, and SvO_2 >65%. This full model was tested at time of diagnosis only, since invasive hemodynamic data at one-year follow-up were not collected per protocol and absent in the majority of patients. Next, a model restricted to non-invasive low-risk criteria (excluding hemodynamics and thus yielding 7 low-risk criteria) was tested both at time of diagnosis and at one-year follow-up within a time-window of six months before and after. Analyses were performed on the original dataset and also after imputation of missing values. Multiple imputation with fully conditional specification (IBM SPSS) was used to impute missing values for variables with <50% missing data which met the 'missing at random' assumption, both at diagnosis and at follow-up.[9] Pooled analyses were performed on 15 imputed datasets, generated using multiple imputation with 20 iterations. For each dataset the number of low-risk criteria per patient was calculated and all the 15 datasets were combined and pooled analysis yielded an average of the total number of low-risk criteria for every patient. Transplant-free survival was the primary outcome variable. Survival according to the number of low-risk criteria at diagnosis and at one-year-follow-up in both the models was assessed with the Kaplan-Meier method,

compared using the log-rank test. Time-dependent receiver operating characteristics analysis of the number of low-risk factors at time of diagnosis according to both the full WSPH 2013 model and the non-invasive model were analyzed with the TimeROC package in R.[10]

58 children (53.4% female) with IPAH/HPAH were included for analyses at time of diagnosis. The median (IQR) age was 6.8 (2.2-13.4) years. The median (IQR) follow-up duration was 3.1 (0.7-8.4) years. At diagnosis more patients were in WHO-FC III (39.7%) or IV (27.6%) than in WHO-FC I-II (32.7%). Figure 1A shows that, using the full WSPH 2013 model, patients with a higher number of low-risk factors had significantly better transplant-free survival (log-rank test p=0.001). Time-dependent receiver operating characteristics (ROC) analysis of the full model for survival status at 5 year follow-up yielded an area under the curve (AUC) of 0.78 (SE 0.07). The optimal threshold value (on a continuous scale of 0-13 low-risk factors) when maximizing sensitivity and negative predictive value was estimated at 10 low-risk factors. Sensitivity: 0.96 (SE 0.04), specificity: 0.46 (SE 0.10), positive predictive value (PPV): 0.57 (SE 0.08), negative predictive value (NPV): 0.93 (SE 0.06). A calibration plot comparing the observed and expected survival for the full WSPH 2013 model showed a good goodness of fit. Using the non-invasive model, children who had all seven low-risk criteria at time of diagnosis, showed 1-, 3- and 5-year survival rates of 100%. In contrast, patients with only three non-invasive low-risk criteria showed 1-, 3- and 5-year survival rates of 69%, 35% and 35% respectively. The higher the number of low-risk criteria present at diagnosis, the better was transplant-free survival (log-rank test p=0.009). Time-dependent ROC analysis of the non-invasive model at 5 year follow-up yielded an AUC of 0.76 (SE 0.07). The optimal threshold value (on a continuous scale of 0-7 non-invasive low-risk factors) when maximizing specificity and PPV was estimated at 4 low-risk factors. Sensitivity: 0.52 (SE 0.11), specificity: 0.83 (SE 0.08), PPV: 0.71 (SE 0.12), NPV: 0.70 (SE 0.08). When setting the threshold value at 5 low-risk factors (which was used in our change

model, Figure 1B) the values are: sensitivity: 0.74 (SE 0.09), specificity: 0.75 (SE 09), PPV: 0.69 (SE 0.10), NPV: 0.79 (SE 0.08). At 1 year follow-up (median 12.5 months; IQR 10.9-13.5), non-invasive measurements were performed in 44 children. Children with 7 non-invasive low-risk criteria at one-year-follow-up had 1-, 3- and 5-year survival rates of 100%, 86% and 86%, whereas those with only 3 low-risk criteria: 33%, 33% and 33% respectively. The higher the number of low-risk criteria present at follow-up, the better was transplant-free survival (log-rank test p=0.009). Children who presented with ≥ 5 out of 7 non-invasive low-risk criteria at diagnosis and retained these at one-year-follow-up had a better prognosis than those who at re-evaluation retained only ≤ 4 low-risk criteria, independent which low-risk criteria were maintained (p=0.003)(Figure 1B). A calibration plot comparing the observed and expected survival for the different change groups showed a good goodness of fit. Importantly, the limited number of study patients did not allow analysis of the individual contribution of each low-risk component and therefore the low-risk components were not weighed. Children who had ≤ 4 low-risk criteria at diagnosis but improved towards ≥ 5 low-risk variables at the time of re-evaluation had a better transplant-free survival compared to those who maintained having ≤ 4 low-risk criteria at follow-up.

These findings in a national cohort of children with PAH are in line with those in a French national cohort of adults with PAH. Boucly et al. found that risk assessment both at diagnosis and at first re-evaluation, using criteria proposed in the 2015 ESC/ERS guidelines for adults with PAH, accurately predicted prognosis.[11] In the current study, time-dependent ROC analyses yielded AUCs of >0.7 for both the full WSPH 2013 and the non-invasive model, indicating fair models. The full model was especially accurate in identifying those patients who were at lower risk for mortality. Patients with 10 or more low-risk factors had better survival than patients with less than 10 low-risk factors. This can be used for clinicians when treating children with PAH. From the non-invasive model, the results of sensitivity,

specificity, PPV and NPV were not optimal, which means that this model needs optimization. Our results further suggest that preserving or reaching a low-risk profile at follow-up may be valuable as a treatment goal in pediatric PAH. However, it is important to keep in mind that the observed association between a change in number of low-risk criteria and outcome not necessarily indicates that such change can be achieved by up titration of PAH-targeted therapies.[12]

The sample size in the current study is relatively small for testing predictive models with multiple variables, limiting statistical power and confidence. Also, the tested models do not have an optimal discriminative power. Improving the discriminative power of both models could be reached with using weighing factors, increasing the contribution of more sensitive variables (from univariable Cox regression analysis) with a weighing system.[13,14] Validation of the current findings in a separate cohort of children with PAH is necessary.

This study suggests that both the full WSPH 2013 pediatric risk stratification tool and a simplified, non-invasive pediatric risk model indeed predicted outcome in children with IPAH/HPAH. Also, preserving or reaching a low-risk profile at follow-up, was associated with improved survival and may thus serve as a treatment goal in pediatric PAH.

References

1. Ivy DD, Abman SH, Barst RJ, Berger RMF, Bonnet D, Fleming TR, Haworth SG, Raj JU, Rosenzweig EB, Schulze Neick I, Steinhorn RH, Beghetti M. Pediatric pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl.):D117-26. doi:10.1016/j.jacc.2013.10.028
2. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL,

Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL. *Pediatric Pulmonary Hypertension*. Vol 132.; 2015. doi:10.1161/CIR.0000000000000329

3. Ploegstra MJ, Zijlstra WMH, Douwes JM, Hillege HL, Berger RMF. Prognostic factors in pediatric pulmonary arterial hypertension: A systematic review and meta-analysis. *Int J Cardiol*. 2015;184(1):198-207. doi:10.1016/j.ijcard.2015.01.038
4. van Loon RLE, Roofthooft MTR, Delhaas T, van Osch-Gevers M, ten Harkel ADJ, Strengers JLM, Backx A, Hillege HL, Berger RMF. Outcome of Pediatric Patients With Pulmonary Arterial Hypertension in the Era of New Medical Therapies. *Am J Cardiol*. 2010;106(1):117-124. doi:10.1016/j.amjcard.2010.02.023
5. Ploegstra M-J, Roofthooft MTR, Douwes JM, Bartelds B, Elzenga NJ, van de Weerd D, Hillege HL, Berger RMF. Echocardiography in Pediatric Pulmonary Arterial Hypertension: Early Study on Assessing Disease Severity and Predicting Outcome. *Circ Cardiovasc Imaging*. 2014;8(1):e000878-e000878. doi:10.1161/CIRCIMAGING.113.000878
6. Jone P-N, Schäfer M, Li L, Craft M, Ivy DD, Kutty S. Right Atrial Deformation in Predicting Outcomes in Pediatric Pulmonary Hypertension. *Circ Cardiovasc Imaging*. 2017;10(12):e006250. doi:10.1161/CIRCIMAGING.117.006250
7. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;37(1):67-119. doi:10.1093/eurheartj/ehv317
8. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G,

Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2015;46(4):903-975. doi:10.1183/13993003.01032-2015

9. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16(3):219-242. doi:10.1177/0962280206074463

10. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics*. 2000;56(2):337-344. doi:10.1111/j.0006-341X.2000.00337.x

11. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, Picard F, De Groote P, Jevnikar M, Bergot E, Chaouat A, Chabanne C, Bourdin A, Parent F, Montani D, Simonneau G, Humbert M, Sitbon O. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*. 2017;50(2):1-10. doi:10.1183/13993003.00889-2017

12. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL, Mark DB, Piña IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide–guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA - J Am Med Assoc*. 2017;318(8):713-720. doi:10.1001/jama.2017.10565

13. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and

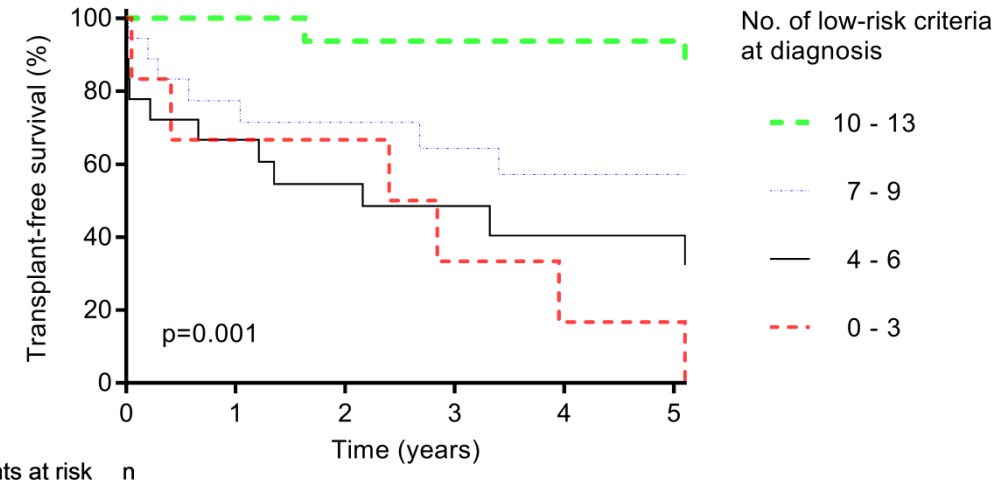
long-term pulmonary arterial hypertension disease management (REVEAL). *Circulation*. 2010;122(2):164-172. doi:10.1161/CIRCULATIONAHA.109.898122

14. Benza RL, Gomberg-Maitland M, Miller DP, Frost A, Frantz RP, Foreman AJ, Badesch DB, McGoon MD. The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest*. 2012;141(2):354-362. doi:10.1378/chest.11-0676

Figure legends

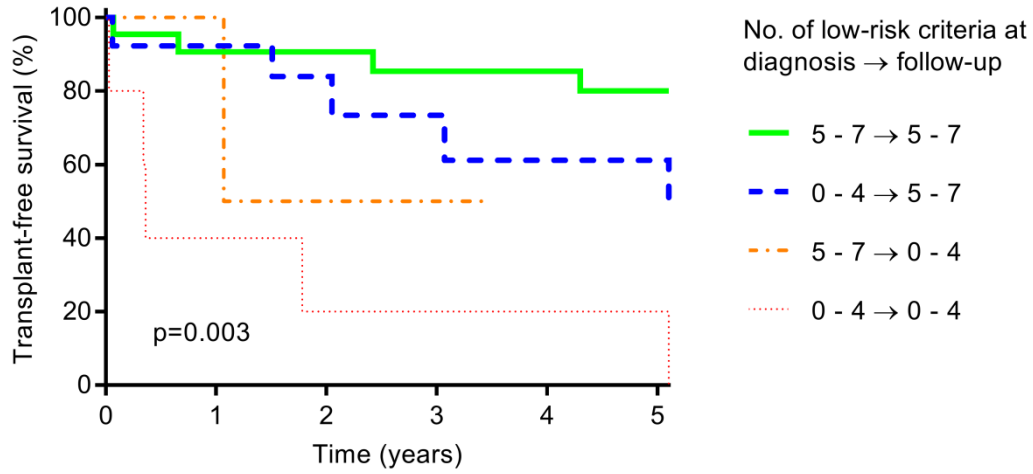
Figure 1 (A) Transplant-free survival according to the full WSPH 2013 pediatric risk stratification model, **(B)** transplant-free survival according to the change in number of low-risk criteria between baseline and one-year-follow-up for the non-invasive model.

A



Patients at risk	n					
10-13	16	16	13	12	11	11
7-9	18	13	11	9	8	7
4-6	18	11	9	7	5	5
0-3	6	4	4	2	1	1

B



Patients at risk	n					
5-7 → 5-7	22	19	17	16	16	14
0-4 → 5-7	14	12	8	6	5	5
5-7 → 0-4	3	2	1	1	0	0
0-4 → 0-4	5	2	1	1	1	1